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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,813	12/24/2003	Nagarajan Ramesh	3802-068-27 CIP	1728

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Supervisor, Patent Prosecution Services
PIPER RUDNICK LLP
1200 Nineteenth Street, N.W.
Washington, DC 20036-2412

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,813	RAMESH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 72-95 is/are pending in the application.

4a) Of the above claim(s) 72-87 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 88-95 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 24 December 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/18/04;4/26/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

1. Claims 72-87 drawn to methods of treating bladder cancer using compositions comprising an oncolytic virus and a transduction enhancing agent that is a mono-,di-, or poly-saccharide with a lipophilic substituent, classified in class 514, subclass 74.
2. Claims 88-95, drawn to methods of treating bladder cancer using compositions comprising an oncolytic virus and a transduction enhancing agent that is a sodium salt of a sulfate ester i.e. general formula I of claim 88, or a 1-sulfo, 4-alkyl benzene sodium salt, i.e. general formula II of claim 88, classified for example in class 514, subclass 20.

The inventions are distinct, each from the other because of the following reasons:

Inventions 1 and 2 rely on structurally distinct transduction enhancing agents. A search of the mono-, di-, or poly-saccharides of group 1 will not overlap with either of the 1-sulfate, 4-alkyl benzene sodium salt or the 1-alkyl sulfate sodium salt of group 2.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter, and because each invention requires a separate, non-coextensive search, restriction for examination purposes as indicated is proper.

During a telephone conversation with Linda Judge on 8/8/05 a provisional election was made without traverse to prosecute the invention of group 2, claims 88-95.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 72-87 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 88-95 are under consideration in this Office Action.

Claim Objections

Claims 88 and 95 are objected to because "luminal" is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a superficial bladder tumor in the mucosal layer of the lumenal surface of a bladder by contacting the lumenal surface of the bladder with a transduction enhancing agent according to formula I or II in claim 88, and subsequently or simultaneously contacting the tumor with an oncolytic virus,

does not reasonably provide enablement for methods of treating bladder cancer in the muscular layer of the bladder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 88-95 are directed to methods of treating cancer of the bladder by contacting the lumenal surface of the bladder with a composition comprising an oncolytic virus and a transduction enhancing agent that is sodium salt of a sulfate ester i.e. general formula I of claim 88, or a p-alkyl benzene sulfonate, i.e. general formula II.

The claims embrace any type of bladder cancer including superficial tumors and invasive cancers affecting the muscular layer of the bladder.

Mullen et al (Oncologist 7:106-119, 2002) taught that the concept of using oncolytic viruses in the treatment of cancer was recognized in the 1940s and 1950s. See page 106, paragraphs bridging columns 1 and 2. Sutton et al (Mol. Ther. 2(3): 211-217, 2000) taught non-replicative (non-oncolytic) adenovirus-mediated suicide gene therapy of orthotopic bladder cancer by direct administration to the tumor. See abstract. Cozzi et al (FASEB J. (March 5, 2001) 10.1096/fj.00-0533fje) taught intravesicular oncolytic viral therapy with an attenuated, replication-competent, herpes simplex virus in an orthotopic model. See entire document. Tumors were generated by intravesicular inoculation with tumor cells leading to superficial tumors accessible by lumenal delivery. See page 5, first paragraph.

Sutton (2000) also taught that administration of adenoviral vectors to the lumenal surface of the bladder resulted in transduction of only the most superficial layers of the

bladder mucosa, and did not result in penetration to an intramuscular tumor. See abstract, and paragraph bridging columns 1 and 2 on page 214.

The instant specification showed that pretreatment of bladders with a p-alkyl benzene sulfonate surfactant led to adenoviral infection of essentially only the surface layer of cells. See Figs 30B. There is no evidence of viral penetration to the muscular layer.

The specification provided no guidance as to how to obtain oncolytic viral transduction of tumors located in the muscle of the bladder by contacting the lumenal surface of the bladder.

Thus one of skill in the art would not have reasonably expected to be able to use the claimed invention to treat bladder tumors other than superficial tumors located in the mucosal layer of the lumenal surface of the bladder. Due to the lack of guidance and examples in the specification, and the state of the art, one would have had to perform undue experimentation in order to practice the claimed method commensurate in scope with the claims, i.e. to treat tumors of the muscular layer of the bladder by administration of oncolytic viruses to the lumenal surface of the bladder.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Cancer Res. 62: 3743-3750, 2002), in view of Heidrun et al (US Patent 5,789,244).

Zhang taught that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33 X 10^9 pfu in combination with docetaxel. See abstract.

Zhang did not teach administration to the lumenal surface of the bladder, or the use of a transduction enhancing agent that was an sodium alkyl sulfate salt.

Heidrun taught methods of treating bladder cancer by intravesical administration of adenoviral vectors. See entire document, e.g. column 2, lines 32-46, and column 7, lines 13-21. Heidrun taught that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycosaminoglycan layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate. See column 5, lines 16-28 and 36-41. Delivery enhancing agents were administered either with, or prior to, adenovirus. See column 6, lines 49-67. Heidrun also suggested adenovirus titres of as high as 5X 10^{10}. See column 6, lines 50-55.

It would have been obvious to of one of ordinary skill in the art at the time of the invention to modify the method Zhang by applying the adenovirus to the lumenal surface of a bladder, as taught by Heidrun, in order to treat bladder cancer. One would have been motivated to use the virus in vivo because this was the whole point of producing the virus (see last sentence of Zhang abstract). One would have been motivated to use lumenal delivery because this allows direct access to superficial

tumors, and because Zhang points out that urethral access to bladder tumors (which leads to lumenal administration) makes bladder tumors appealing targets for viral therapy. It would have been similarly obvious to modify the method of Zhang by treating mouse bladders with sodium lauryl sulfate. One would have been motivated to do so to improve access to tumors in the bladder epithelium. The cited art suggests a range of virus concentrations overlapping the claimed lower limit, so the claimed concentration is prima facie obvious.

The combined references do not teach the use of 0.1 wt. % or less of sodium lauryl sulfate. However, MPEP 2144.05 IIA indicates that differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case it is clear that the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

Claims 88-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Heidrun et al (US Patent 5,789,244) and Mullen et al (Oncologist 7:106-119, 2002).

Watanabe taught treatment of bladder cancer with replication deficient adenovirus carrying a suicide gene in an orthotopic mouse model of bladder cancer.

The adenovirus carried a dominant negative version of *ras*, was instilled intravesically, and inhibited the growth of superficial tumors. 10^9 plaque forming units of adenovirus were delivered. See abstract; page 714, column 1, paragraphs 2 and 3; page 715, column 1, first two full paragraphs; and Fig. 4 on page 715.

Watanabe did not teach an oncolytic virus, or the use of a transduction enhancing mono-, di-, or poly-saccharide having a lipophilic substituent.

Heidrun taught methods of treating bladder cancer by intravesical administration of adenoviral vectors. See entire document, e.g. column 2, lines 32-46, and column 7, lines 13-21.

Heidrun taught that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycosaminoglycan layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate. See column 5, lines 16-28 and 36-41. Delivery enhancing agents were administered either with, or prior to, adenovirus. See column 6, lines 49-67. Heidrun also suggested adenovirus titres of as high as $5X\ 10^{10}$. See column 6, lines 50-55.

Mullen taught that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication deficient gene therapy vectors because the virus amplifies itself through several rounds of replication allowing a concomitant increase in transgene expression leading to an amplified antitumor effect. See page 108, column 1, first full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Watanabe by treating the mouse bladders with

sodium lauryl sulfate and to substitute replication competent adenoviruses for replication deficient ones. One would have been motivated to use sodium lauryl sulfate to improve access to superficial tumors in the bladder epithelium by disrupting the glycosaminoglycan layer of the bladder epithelium, as taught by Heidrun. One would have been motivated to substitute an oncolytic virus for the replication deficient virus in order to take advantage of an amplified antitumor effect due to viral replication, as taught by Mullen. The cited art suggests a range of virus concentrations overlapping the claimed lower limit, so the claimed concentration is prima facie obvious.

The combined references do not teach the use of a pretreatment using 0.1 wt. % or less of sodium lauryl sulfate. However, MPEP 2144.05 IIA indicates that differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case it is clear that the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

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Gaffar taught that sodium lauryl sulfate and sodium dodecyl benzene sulfonate are anionic surfactants with similar performance characteristics. See column 12, line 61 to column 13, line 9.

It would have been obvious to of one of ordinary skill in the art at the time of the invention to modify the method Zhang by applying the adenovirus to the lumenal surface of a bladder, as taught by Heidrun, in order to treat bladder cancer. One would have been motivated to use the virus in vivo because this was the whole point of producing the virus (see last sentence of Zhang abstract). One would have been motivated to use lumenal delivery because this allows direct access to superficial

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The combined references do not a pretreatment using 0.1 wt. % or less of a transduction enhancing agent. However, MPEP 2144.05 IIA indicates that differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case is clear that the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

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the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.